Exhibit 35

Letters

RESEARCH LETTER

Expenditures and Prices of Antihyperglycemic Medications in the United States: 2002-2013

A recent study demonstrated widespread substitution of analog for human insulin and rising out-of-pocket costs in privately insured people with type 2 diabetes in the United States.[1] Medicaid reimbursements have increased for both human insulin and more costly analog insulins.[2] Although studies have described per-person changes in excess medical spending of US adults with diabetes on prescription medications,[3] they have not reported trends in expenditures for different classes of antihyperglycemic medications that simultaneously consider changes in use and price.

Methods | We analyzed individual and prescription-level data from the Medical Expenditure Panel Survey (MEPS) to describe and compare trends in expenditure and price of antihyperglycemic medications in the United States from 2002 through 2013. The MEPS involves deidentified, publicly available data of a nationally representative household survey of noninstitutionalized residents.[4] The in-person interview response rate ranged from 69.2% to 58.0%. We first described the prevalence of treated patients with diabetes, their characteristics, and use of antihyperglycemic medications. We then estimated inflation-adjusted expenditures per patient for insulin (combining both human and analog) compared with other classes of antihyperglycemic medications. Medications were identified using

Table. Weighted Characteristics of Treated Patients With Diabetes in the Medical Expenditure Panel Survey (MEPS), 2002-2013

Characteristics	MEPS Survey Years			
	2002-2004 (n = 5799)[a]	2005-2007 (n = 6486)	2008-2010 (n = 7237)	2011-2013 (n = 8356)
Treated diabetes, % (95% CI)[b]	5.2 (4.9-5.4)	6.2 (5.9-6.5)	7.1 (6.8-7.4)	7.7 (7.4-8.0)
Age, mean (SD), y	60.2 (15.0)	60.3 (14.6)	60.3 (14.8)	60.7 (14.6)
Men, No. (%)	2496 (47.7)	2850 (48.3)	3182 (47.9)	3845 (50.0)
Race, No. (%)[c]				
White	2951 (65.3)	3209 (65.0)	3089 (64.9)	3210 (62.0)
Black	1202 (16.2)	1350 (15.1)	1805 (15.0)	2197 (15.5)
Hispanic	1334 (12.5)	1533 (13.5)	1699 (12.9)	2202 (15.1)
Others	312 (6.1)	394 (6.5)	644 (7.2)	747 (7.4)
Use of medications, % (95% CI)				
Insulin	28.1 (26.2-29.8)	24.1 (22.4-25.8)	25.3 (23.7-27.0)	29.2 (27.6-30.8)
Metformin	36.1 (34.2-38.0)	43.6 (41.6-45.5)	47.3 (45.4-49.2)	51.5 (49.8-53.1)
Sulfonylureas	38.2 (36.2-40.1)	35.1 (33.2-36.9)	30.7 (28.9-32.4)	27.5 (25.8-29.3)
Thiazolidinediones	21.1 (19.5-22.7)	23.2 (21.5-24.9)	13.0 (11.6-14.3)	5.8 (5.0-6.6)
α-Glucosidase inhibitors and nonsulfonylurea secretagogues	2.6 (2.0-3.2)	2.8 (2.2-3.4)	1.4 (1.0-1.8)	0.7(0.5-1.0)
DPP-4 inhibitors		1.2 (0.8-1.5)	5.6 (4.7-6.5)	7.7 (6.8-8.7)
Combinations	6.8 (5.8-7.7)	8.9 (7.8-9.9)	8.0 (7.0-9.0)	6.0 (5.1-6.9)
All orals[d]	68.9 (66.9-70.8)	72.6 (70.9-74.4)	70.8 (69.2-72.5)	69.5 (67.9-71.1)
Amylin analogs		0.1 (0-0.1)	0.2 (0.1-0.4)	0.1 (0-0.2)
GLP-1 receptor agonists			2.2 (1.6-2.8)	2.7 (2.1-3.4)
All noninsulin injectables[e]			2.4 (1.8-3.1)	2.8 (2.1-3.4)
Quantity of medications (95% CI)[f]				
Insulin, mL	171 (160-181)	150 (137-164)	205 (191-218)	206 (193-220)
All orals, tablets	611 (580-641)	632 (607-657)	775 (746-804)	800 (772-828)
All noninsulin injections, mL			21 (16-25)	36 (30-42)

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

[a] The reported statistics were based on a pooled sample across 3 waves of MEPS.

[b] Percentage of all survey respondents. People treated for diabetes were identified using 3-digit *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes.

[c] Race was included as part of the descriptive analysis. As defined by MEPS, classification by race and ethnicity was mutually exclusive and based on information reported for each family member. All persons whose main national origin or ancestry was reported as Hispanic, regardless of racial background, were classified as Hispanic.

[d] Included metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, and nonsulfonylurea secretagogues, combinations, and DPP-4 inhibitors.

[e] Included amylin analogs and GLP-1 receptor agonists from 2008.

[f] Quantities of medication used were means per patient per year, conditional on some recorded use of the drug over the given period.

Multum Lexicon therapeutic class codes. Drug expenditures from all sources (including patient co-payments) and quantity used came from household surveys, with data verified by pharmacies. Relative and absolute mean drug prices were calculated by dividing expenditure per prescription by quantity. All analyses were conducted in Stata (StataCorp), version 13.1, accounting for MEPS sampling weights and the complex survey design. The 95% confidence intervals were calculated and compared to determine statistically significant differences.

Results | The unweighted analytic sample consisted of 27 878 people treated for diabetes (mean age, 60.4 years [SD, 14.7]; men, 44.4%). During the study period, the prevalence of treated diabetes increased from 5.2% (95% CI, 4.9%-5.4%) in 2002-2004 to 7.7% (95% CI, 7.4%-8.0%) in 2011-2013 (**Table**). For those with recorded insulin use, the quantity per year increased from 171 mL (95% CI, 160-181) in 2002-2004 to 206 mL (95% CI, 193-220) in 2011-2013; over the same period, estimated spending for insulin per patient increased from $231.48 (95% CI, $190.40-$272.55) in 2002 to $736.09 (95% CI, $639.72-$832.47) in 2013 (**Figure**). In 2013, estimated expenditure per patient amounted to $507.89 (95% CI, $422.34-$593.44) for analog insulin and $228.20 (95% CI, $183.98-$273.42) for human insulin. The total expenditure on insulin in 2013 was significantly greater than the combined expenditure on all other antihyperglycemic medications of $502.57 (95% CI, $430.37-$574.78).

The mean price per milliliter of insulin increased by 197% from $4.34 per milliliter (95% CI, $4.19-$4.51) in 2002 to $12.92 per milliliter (95% CI, $12.34-$13.50) in 2013, whereas the mean price of dipeptidyl peptidase-4 (DPP-4) inhibitors increased by 34% from $6.67 (95% CI, $6.26-$7.09) per tablet in 2006 to $8.92 (95% CI, $8.43-$9.41) in 2013. The mean price of metformin decreased by 93% from $1.24 per tablet (95% CI, $1.19-$1.29) in 2002 to $0.31 per tablet (95% CI, $0.25-$0.36) in 2013.

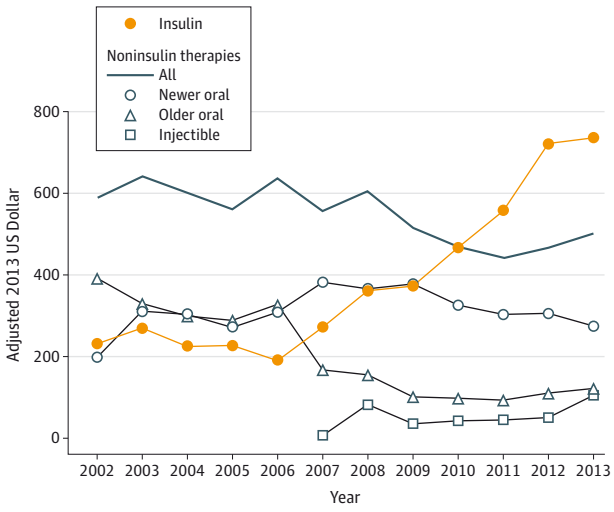
Discussion | Based on a nationally representative survey, the mean price of insulin increased from $4.34 per milliliter in 2002 to $12.92 in 2013. The estimated expenditure per patient for insulin in the United States in 2013 was greater than all other antihyperglycemic medications combined. Another factor contributing to the rise in expenditures on insulin was increased treatment intensity.

The mean price of insulin increased at a much faster rate than oral medications including DPP-4 inhibitors. We were unable to separate out generics from branded medications; however, unlike oral therapies, the mean price of insulin is unlikely to decline as a result of generic competition[5] because of the stringent regulations and substantial costs of bringing biosimilar insulins to market.

Limitations of our study included changes in editing rules for improved price benchmarking of the MEPS prescribed medicines data from 2007.[6] This may have artificially increased the reported drug expenditures by an estimated 10%.[6] Our reported estimates of expenditure and price did not include the cost of the various insulin delivery devices except prefilled pens.

Significant changes in mean price of insulin, relative to comparator therapies, suggest a need to reassess the effectiveness and cost-effectiveness of alternative antihyperglycemic therapies.

Figure. Mean Expenditure per Patient for Antihyperglycemic Medications, 2002-2013



Medications were classified as follows: insulin (human and analog); newer oral therapies (thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and combinations); older oral therapies (metformin, sulfonylureas, α-galactosidase inhibitors, and nonsulfonylurea secretagogues); noninsulin-based injectable therapies (glucagon-like peptide-1 receptor agonists and amylin analogs).

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hua, Carvalho, Herman, Clarke.
Critical revision of the manuscript for important intellectual content: Tew, Huang, Herman, Clarke.
Statistical analysis: Hua, Carvalho, Tew.
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1. Lipska KJ, Ross JS, Van Houten HK, Beran D, Yudkin JS, Shah ND. Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. *JAMA*. 2014;311(22):2331-2333.

2. Luo J, Avorn J, Kesselheim AS. Trends in Medicaid reimbursements for insulin from 1991 through 2014. *JAMA Intern Med*. 2015;175(10):1681-1686.

3. Zhuo X, Zhang P, Kahn HS, Bardenheier BH, Li R, Gregg EW. Change in medical spending attributable to diabetes: national data from 1987 to 2011. *Diabetes Care*. 2015;38(4):581-587.

4. Agency for Health Care Research and Quality. MEPS HC-155: 2012 full year consolidated data file. http://meps.ahrq.gov/mepsweb/data_stats/download_data/pufs/h155/h155doc.pdf. Accessed September 23, 2015.

5. Greene JA, Riggs KR. Why is there no generic insulin? historical origins of a modern problem. *N Engl J Med*. 2015;372(12):1171-1175.

6. Agency for Health Care Research and Quality. Comparison of retail drug prices in the MEPS and MarketScan: implications for MEPS editing rules. http://meps.ahrq.gov/mepsweb/data_files/publications/workingpapers/wp_10001.pdf. Accessed July 29, 2015.

COMMENT & RESPONSE

Breast Cancer Screening: Benefit or Harm?

To the Editor In the systematic review of breast cancer screening, Dr Myers and colleagues[1] claimed that our Cochrane review[2] showed that breast screening reduces cause-specific mortality by 19%, there was no significant heterogeneity, and our results were similar to those of other reviews. This misrepresents our findings and creates an impression of scientific agreement that does not exist.

It is also not correct that our estimate that 10 women were overdiagnosed for each avoided death from breast cancer was based on "all trials." We documented important methodological differences and pronounced heterogeneity between results of poorly and adequately randomized trials (I^2 = 78%). Trials with adequate randomization found little or no benefit (relative risk, 0.90 [95% CI, 0.79-1.02] for adequately randomized trials vs 0.75 [95% CI, 0.67-0.83] for poorly randomized trials).[2] Other researchers have expressed similar concerns.[3] When study methods provide a compelling explanation for substantial differences in results between studies, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) handbook[4] recommends using the estimates from trials with a lower risk of bias. However, Myers and colleagues did not properly consider the differences in quality of studies when they used GRADE.

The doubtful benefit of breast screening at the population level was confirmed in observational studies from Norway and Denmark, the only countries that allow use of contemporary, same-age control groups.[2] Observational studies without control groups are less reliable, no matter how well designed, and improved therapy can explain the entire observed mortality reduction over the past decades.[5] When the benefit is overestimated, Cancer Intervention and Surveillance Modeling Network models of the balance between benefits and harms become misleading.[1]

The new American Cancer Society (ACS) guidelines are a step in the right direction but the insights that led to the recommendations are not new and they do not fully adopt the evidence-based approach. Overconfidence in flawed trials, fueled by economic conflicts of interest and good intentions, has led to many women being given diagnoses of breast cancer that they did not need, producing unwarranted fear and psychological stress and exposing them to treatment that can only harm them. Treatment of overdiagnosed, healthy women kills many of them, and total mortality is therefore the proper outcome. Screening has not reduced total mortality,[2] and it is therefore misleading to claim that "screening saves lives." If recommendations are based on poor evidence, rather than the most reliable trials, interventions will continue to be used that lead to much harm, with little or no benefit.

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1. Myers ER, Moorman P, Gierisch JM, et al. Benefits and harms of breast cancer screening: a systematic review. *JAMA*. 2015;314(15):1615-1634.

2. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev*. 2013;6:CD001877.

3. Jüni P, Zwahlen M. It is time to initiate another breast cancer screening trial. *Ann Intern Med*. 2014;160(12):864-866.

4. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook. http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html. Accessed October 29, 2015.

5. Dowsett M, Forbes JF, Bradley R, et al. Aromatase inhibitors vs tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-1352.

In Reply In the Cochrane meta-analysis limited to "adequately randomized" trials, the pooled estimate for mortality reduction was 0.90 (95% CI, 0.79-1.02).[1] We included the results of this more restrictive analysis in presentations of our results to the ACS Guidelines Development Group. Although we agree that variation in study design or conduct may result in some bias in estimate within the randomized trials, we share the judgment of the UK Independent Panel that these are unlikely to substantially affect the estimate, given the general consistency of results,[2] and elected to present the results of meta-analyses that included the same trials primarily for space considerations. We certainly did not intend to imply that there is scientific agreement about the extent by which (or even if) mammography reduces breast cancer mortality. Although some policy makers are using these more restrictive estimates,[3] other groups have put a stronger emphasis on more recent observational studies with a far greater mortality reduction.[4]